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ORIGINAL ARTICLE

The effect of boost radiotherapy on local control in ductal carcinoma in-situ of the breast: Retrospective single-center experience with literature review

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Summary

Purpose: *We aimed to investigate factors related to local recurrence and especially the effects of additional radiotherapy (RT) boost after whole breast radiation therapy (WBRT) on local recurrence in ductal carcinoma in situ (DCIS) patients undergoing breast-conserving surgery (BCS).*

Methods: *In this retrospective analysis, 197 patients treated for DCIS between 1998-2018 were evaluated. Patients with microinvasion, intracystic in situ cancer, undergoing mastectomy, less than 12 months of follow-up, and missing information were excluded.*

Results: *The median age was 50 years (28-78). The median follow-up time was 97 months (12-257). Local recurrence occurred in eight patients (4%), six of them were invasive and two were DCIS. Systemic metastasis was present in a patient who recurred as invasive cancer. Contralateral breast cancer developed in nine patients (4.5%). Boost radiation was given to patients 143 (72.6%). Local recurrence developed in two patients (3.7%) without boost and six patients (4.2%) with boost; there was no significant difference in local recurrence free survival between patients with and without boost radiation (p=0.94). The factors affecting significantly local recurrence were age, tumor diameter, and surgical margin width (≤ 2 mm) in univariate analysis, but only tumor diameter and surgical margin width (≤ 2 mm) in multivariate analysis.*

Conclusion: *Surgical margin width and tumor diameter were independently associated with local recurrence. In contrast, patient age, RT boost, hormonotherapy use, and poor histological features were not significantly associated with local recurrence.*

Key words: *breast cancer; breast-conserving surgery; boost; ductal carcinoma in-situ; local recurrence; radiotherapy*

Introduction

With the increase in mammographic screening programs, ductal carcinoma *in situ* (DCIS) has been increasing worldwide [1]. Randomized trials have shown that local recurrence reduced by an average of 50% with the addition of whole breast radiotherapy (WBRT) to breast-conserving surgery (BCS) [2-4]. The positive effect of WBRT on local recurrence is evident even in the low-grade DCIS [5]. Additionally, studies show that WBRT also has positive effects on survival in high-grade patients [6].

In patients who underwent BCS for invasive breast cancer, a significant reduction in local recur-

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rence was achieved by adding boost radiation to WBRT [7]. While there is strong evidence for the contribution of WBRT to local control, the place of boost radiation in DCIS treatment is controversial due to lower incidence of DCIS compared to invasive cancer, its heterogeneity, low local recurrence rates after WBRT, and the difficulty of performing long-term clinical studies in a large number of patients. Randomized prospective clinical trials which investigate the administration of boost together with WBRT after BCS for DCIS are ongoing, and their results are still expected [8-11].

In our study, we aimed to investigate factors related to local recurrence and especially the effects of additional RT boost after WBRT on local recurrence in DCIS patients undergoing BCS.

Methods

Patient and tumor characteristics

In this retrospective analysis, 241 patients treated for DCIS in Group Florence Nightingale Hospitals between 1998-2018 were evaluated. After excluding patients with microinvasion, intracystic *in situ* cancer, undergoing mastectomy, less than 12 months of follow-up, and missing information, 197 patients were analyzed.

Demographic, clinical, pathological features, treatment and survival characteristics of patients were recorded from patients' charts.

Radiotherapy

The amount of radiation and the area to be applied were determined according to the patient-based decision of an expert breast radiation oncologist. WBRT was planned with 6MV photons from tangential fields using three-dimensional (3D) or field-in-field (FiF) techniques for all patients. Dose inhomogeneity was reduced by using static or dynamic wedges in 3D plans. For boost planning, the tumor bed treatment volume was determined with the appropriate margin, taking into account the area marked with clips, the scar tissue in the breast, and the seroma. Electron field or combined photon-electron fields (electron field combined with 6MV photon mini-tangential fields) with electron energy (6-20MeV) selected according to the appropriate depth for CT were used for RT Boost. One hundred ninety-two patients receiving normofractionated treatment (1.8-2Gy / fraction) received 50Gy (range: 44-50.4Gy) median to the whole breast and 10Gy (range: 4-16Gy) radiotherapy to the tumor bed. In 5 cases who received hypofractionated treatment (2.66Gy / fraction), a median of 40Gy (range: 40-42.5Gy) was given to the whole breast, and 4 of these cases received a boost at 10Gy / 4 fraction.

Follow-up

After the end of the radiotherapy, the patients were followed-up by their surgeons and radiation oncologists at 3-6 months intervals for the first three years and at least once a year thereafter with physical and radiologi-

Table 1. Patient characteristics

	Number (%)
Age (years, median)	50 (28-78)
<50	91 (46.2)
≥50	106 (53.8)
Menopausal status	
Pre-menopausal	89 (45.2)
Post-menopausal	106 (53.8)
Unknown	2 (1)
Tumor size (mm median)	15 (2-75)
≤20	141 (71.6)
>20	56 (28.4)
SLNB	
Yes	123 (62.4)
No	74 (37.6)
ALND	
Yes	9 (4.6)
No	183 (92.9)
Unknown	5 (2.5)
Surgical margin width (mm)	
≤2	35 (17.8)
>2	162 (82.2)
Nuclear grade	
NG I	25 (12.7)
NG II	58 (29.4)
NG III	94 (47.7)
Unknown	20 (10.2)
Comedo necrosis	
No	77 (39.1)
Yes	95 (48.2)
Unknown	25 (12.7)
ER status	
Negative	22 (11.2)
Positive	158 (80.2)
Unknown	17 (8.6)
PR status	
Negative	46 (23.4)
Positive	129 (65.5)
Unknown	22 (11.2)
HER-2 status	
Negative	47 (23.9)
Positive	18 (9.1)
Unknown	103 (52.3)
RT boost	
No	54 (27.4)
Yes	143 (72.6)

RT: radiotherapy, ER: estrogen receptor, PR: progesterone receptor, SLNB: sentinel lymph node biopsy, ALND: axillary lymph node dissection

cal examinations when deemed necessary. In the absence of any symptoms, each patient was followed up by having a mammography a year.

Statistics

Categorical variables of patient and tumor characteristics were compared using Pearson's correlation method or Mann-Whitney U test as appropriate. The log-rank test was used for comparison of differences between survival curves that were derived by the Kaplan-Meier method. Cox proportional hazard regression was used to model clinical outcomes such as local recurrence-free survival (LRFS) and disease-free survival (DFS) after breast-conserving surgery. All p values from two-sided tests and a p value ≤0.05 were considered statistically significant. Statistical analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL).

Results

The median age of 197 patients was 50 years (28-78). All patients underwent BCS. The axillary staging was performed in 132 (67%) patients. Axillary lymph node dissection (ALND) was the preferred method for axillary staging before the establishment of sentinel lymph node biopsy (SLNB). No metastasis in lymph nodes was detected in axillary staging (Table 1). Re-excision was performed in 14 patients (7%) due to positive surgical margins. Approximately half of the patients (42.1%) had low or intermediate grade. Hormone receptor positivity was present in 80% of patients, and they received tamoxifen. The median follow-up time was 97 months (12-257). 37% of the patients were followed for more than five years, 37% for more than ten years.

Local recurrence occurred in eight patients (4%), six of them were invasive and two were DCIS. The median time to local recurrence was 104.5 months (10-180). Systemic metastasis was also present in a patient who recurred as invasive cancer. Contralateral breast cancer developed in nine patients (4.5%) during follow-up. Four patients died due to reasons other than breast cancer. 10-year breast cancer-specific survival, disease-free survival, and local recurrence-free survival were 100%, 92.5%, 96%, respectively.

Boost radiation was given to 143(72.6%) patients. The patients undergoing additional boost had significantly more comedo necrosis, higher nuclear grade, and closer surgical margins (<2mm). Local recurrence developed in two patients (3.7%) without boost and six patients (4.2%) with boost (Table 2). In Kaplan-Meier analyses, there was no significant difference in local recurrence between patients with and without boost radiation (p=0.94) (Figure 1).

The factors affecting local recurrence were investigated, and age, tumor diameter, and surgical margin width closer than 2 mm were significantly related to local recurrence in univariate analysis. In multivariate analyses, tumor diameter and sur-

Table 2. Patient characteristics with and without boost

	RT Boost (-) n (%)	*RT Boost (+) n (%)*	*p value*
Tumor size, cm			0.55
≤2	37 (68.5)	104 (72.7)	
>2	17 (31.5)	39 (27.3)	
Age, years			0.9
≤50	25 (46.3)	66 (46.2)	
>50	29 (53.7)	77 (53.8)	
Nuclear grade			0.004*
I+II	33 (63.5)	50 (40)	
III	19 (36.5)	75 (60)	
Comedo Necrosis			0.001*
No	33 (63.5)	44 (36.7)	
Yes	19 (36.5)	76 (63.3)	
Hormone receptor status			0.052
Positive	49 (96.1)	110 (85.9)	
Negative	2 (3.9)	18 (14.1)	
Surgical margin width, mm			0.002*
≤2	2 (3.7)	33 (23.1)	
>2	52 (96.3)	110 (76.9)	
Hormone therapy			0.30
No	8 (16.3)	30 (23.4)	
Yes	41 (83.7)	98 (76.6)	
Local recurrences			
Yes	2 (3.7)	6 (4.2)	
No	52 (96.3)	137 (95.8)	

*Chi-square test

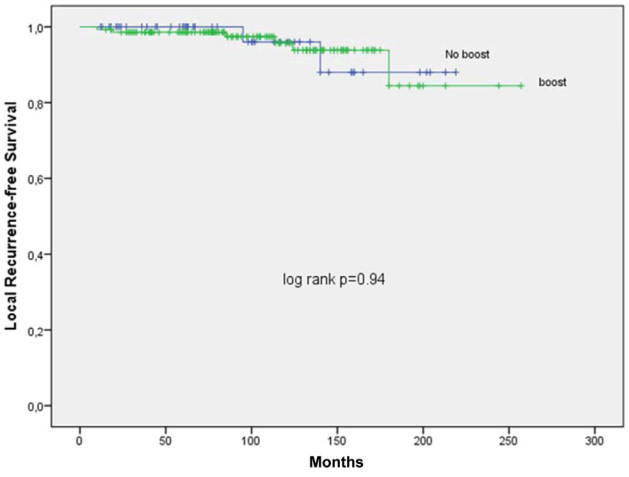

Figure 1. LFRS between patients with and without boost.

gical margin width closer than 2 mm appeared as only factors that independently related with local recurrence (Table 3).

Discussion

The importance of postoperative radiotherapy in patients undergoing breast-conserving surgery for DCIS has been demonstrated by numerous randomized clinical trials [4]. However, whether boost RT is beneficial in these patients is not as certain as in invasive cancer. It is challenging to plan a randomized clinical trial due to reasons such as the rarity of DCIS compared to invasive cancer, the relatively rare local recurrence after RT in patients with DCIS, and the need for a long follow-up time. When the literature is examined, it is seen that different results were obtained in 11 retrospective studies evaluating RT boost for DCIS [10-20] (Table 4). Omlin et al [10] showed significant effects of RT boost on local recurrence in a multicentre study in which only patients under 45 years of age were evaluated. However, in this study, there were many unknown data on variables that may affect local recurrence, such as tumor diameter, nuclear grade, and surgical margin width. The effect of RT boost could not be demonstrated in the study by Yerushalmi et al [11]. However, this study did not include pure DCIS cases, and 16% of patients also had micro-invasive cancer accompanying DCIS, and only the patients who had close (<1mm) margins and micro-invasive disease received boost radiation therapy. Monteau et al [12] compared patients who underwent re-excision + RT with those who underwent RT and boost without re-excision among patients with near or positive margins, and no significant difference was found between the two groups in terms of local recurrence. In the study of Wai et al [13], the patients were divided into three groups that received different treatments (local excision (LE), LE+RT, and LE+RT+Boost) and compared, and the results showed that boost radiation did not have any positive effect on local recurrence but there were more surgical margin positivity, more advanced nuclear grade, and more necrosis in the LE + RT + boost group. In a study conducted by Wong et al [14] the positive effects of adding boost on local recurrence in a median 3.8 years follow-up

Table 3. Univariate and Multivariate analysis of ipsilateral breast tumor recurrence

	Univariate analysis			*Multivariate analysis*		
	HR	95% CI	p	*HR*	*95% CI*	*p*
Age, years	0.89	0.81-0.98	0.02	0.92	0.84-1.004	0.06
Tumor size	1.04	1.008-1.09	0.019	1.04	1.002-1.087	0.048
NG (I+II vs III)	271	0.52-14.04	0.23			
Comedo necrosis	4.76	0.55-41.01	0.15			
RT boost (yes vs. no)	1.72	0.28-10.33	0.55			
Surgical margin ≤2 mm	5.04	1.2-20.2	0.023	5.41	1.06-18.4	0.041

Table 4. Result of previous studies with BCS+RT with and without boost

Author	*Patients with boost n (%)*	*Median age, years n (%)*	*Clear surgical margins*	*Median follow up (years)*	*LRFS (%-With & without boost)*	*Effect of boost on IBTR*
Omlin et al., 2006	316 (52)	41 (23-45)	65	6.0	72 vs 86	Yes
Yerushalmi et al, 2006	75 (25.0)	58 (39-88)	37	6.8		No
Jiveliouk et al., 2009	107 (37.3)	51 (32-81)	81	4.0	100 vs. 100	No
Monteau et al., 2009	208 (71.0)	53 (28-82)	-	7.4	96 vs. 95	Yes
Wai et al., 2011	482 (29.8)	55	87	9.3	96 vs. 93	No
Wong et al., 2012	220 (36.0)	-	78	3.8	-	Yes
Rakovitch et al., 2013	1895 (29.6)	56 (20-85)	58	10.0	88 vs. 87	No
Meattini et al., 2013	389 (48.8)	-	95	7.7	-	Yes
Kim et al., 2014	728 (31.9)	46 (19-72)	54 (≥2mm)	6.7	98.5 vs. 95.4	No
Cutuli et al., 2016	819 (48.0)	56 (32-84)	48	7.5	-	No
Moran et al., 2017	4131 (64.4)	56	87	9.0	97.1 vs. 96.3	Yes
Current study	143 (72.6)	50 (28-78)	97	8	95.7 vs. 96	No

period were shown in univariate analysis. Since RT boost was not included in the multivariate analysis, its independent effect on local recurrence was not reported. In the study conducted by Rakovitch et al [15] in which 1895 patients were followed for a median of 10 years, local recurrence was 13% in the RT boost group and 12% in the group without RT boost (HR = 0.82, 95% CI 0.59-1.15). In the study of Meattini et al [16], it was shown that adding boost to RT and wider surgical margins significantly reduced the risk of local recurrence in multivariate analysis, although no significant effect was detected in univariate analysis. In a Korean multicentre study conducted by Kim et al [17], 728 patients were followed for a median of 6.7 years, and the effect of RT boost on local recurrence could not be demonstrated. In this study, the nuclear grade was significantly higher in the RT boost group. The effect of RT boost on local recurrence could not be demonstrated in the subgroup analysis in which only patients under the age of 40 or patients with close (<2 mm) surgical margins were examined. In a multinational study conducted by Cutili et al [18] with eight centres, no significant effect of RT boost on local recurrence was shown. In this study, it is noteworthy that approximately 60% of the patients had a tumor diameter less than 1 cm, and the number of patients with high nuclear grade and comedo necrosis was relatively low. On the other hand, in a multicentre retrospective study by Moran et al [19] involving 4131 patients, a significant decrease in local recurrence was found in the RT boost group (HR 0.73; 95% CI, 0.57-0.94). Another study by Jiveliouk et al [20] showed no effect of adding boost RT. In that study, 107 consecutive women who underwent BCS with diagnoses of DCIS in mammographic screening were observed and followed for 52 months. No recurrences were observed in both arms. In the NSABP 24 study examining the effects of tamoxifen on local recurrence [21], 692 patients were given RT boost, and no significant effect of RT boost on local recurrence was shown [22]. Our study included 197 consecutive patients treated in a single-centre, and our median follow-up time was 97 months. No relationship was found between RT boost and local recurrence. There were significantly higher nuclear grade, more comedo necrosis, and closer surgical margins in the RT boost group in our study. As in the studies conducted by Wai et al [13] and Monteau et al [12], it can be assumed that the local recurrence risk was downgraded by adding the RT boost to patients with closer surgical margins, and local recurrence rates were reduced to the level of patients with wider excision. Our findings are also concordant with the preliminary results of BIG 3-07/TROG 07.01 randomized trial published in San-Antonio Breast Cancer Symposium 2020. In that trial, non-low risk DCIS patients undergoing BCS+ boost RT had significantly lower local recurrence rates than patients with BCS+ conventional RT in a median 6.6 years follow-up [23].

Although multifocality is common in DCIS, multicentricity is rarely seen [24,25]. Holland et al [24] detected a second focus 4 cm away from the primary lesion in only 1 of the 32 patients they investigated. Besides, the tumor diameter measured radiologically in roughly half of the patients was smaller than the pathological diameter. In a study conducted by Faverly et al [25], skip lesions were detected at a distance of 0-5 mm from the primary tumor in 82% of the patients and more than 10 mm in 8%. In another study, 56% of 61 patients who underwent re-excision due to close (<2 mm) surgical margin had residual disease [12]. For these reasons, the ideal surgical margin width in patients who underwent breast-conserving surgery with a DCIS diagnosis has been a controversial topic for decades but it is very well known that patients with a negative surgical margin are at a lower risk of local recurrence than patients who are positive [4]. Since the relationship between surgical margin width and local recurrence was not investigated in 4 randomized prospective studies investigating the effects of WBRT on local recurrence after local excision, there is no randomized clinical study conducted on this subject [2,26-28]. Silverstein et al [29] showed that recurrences after DCIS originated from the area of the primary lesion; therefore, RT may not be needed in lesions excised sufficiently large (> 1 cm). This hypothesis is still controversial. Although it is accepted that some DCIS cases can be treated with BCS, but without RT, discussions on the definition of this subgroup continue. In a single-arm study conducted by Wong et al [30], a high local recurrence rate of 12% in 5 years follow-up was found in patients who underwent only local excision with a surgical margin> 1 cm. In another study in which approximately 3000 patients were evaluated, significant relationship between surgical margin width and local recurrence was shown only in patients who did not receive RT. However, it could not be shown in patients undergoing RT [31]. A meta-analysis including 7886 patients who underwent LE+RT showed that margins wider than 2 mm surgical did not reduce the risk of local recurrence. However, local recurrence risk increased significantly, with a margin width of 0-2 mm [32]. In our study, a surgical margin width of 2 mm or less was independently associated with local recurrence. Our findings are in line with the Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clini-

cal Oncology Consensus Guideline published in 2016 [33].

In the multivariate analysis of a prospective non-randomized study of 665 patients who underwent only local excision due to DCIS, tumor diameter, and high nuclear grade were identified as independent factors affecting local recurrence [34]. In a study by Silverstein et al [29], the presence of comedo necrosis, high nuclear grade, and tumor diameter were associated with local recurrence in addition to the close surgical margin. In our study, tumor size was associated with local recurrence, but the effect of being high grade or the presence of comedo necrosis on local recurrence was not shown.

SEER data, in which more than 200,000 women with invasive breast cancer were examined, showed that women younger than 40 years had higher grade and hormone receptor-negative breast cancer phenotype, and younger age had independent adverse effects on survival [35]. The relationship between young age and aggressive tumor phenotype has also been shown in women with DCIS [36]. In the EORTC 10853 study, it was found that the risk of local recurrence was almost twice as high in patients younger than 40 years of age undergoing breast-conserving surgery due to DCIS [26]. Similarly, Cronin et al [37] found that in the retrospective analysis of 2996 patients, local recurrence was reduced by approximately half in those older than 50 years of age. In the NSABP B 17 study conducted by Fisher et al, no relationship was found between age at the time of diagnosis and tumor recurrence [27]. In our study, a significant relationship was found between young age and local recurrence in univariate analysis, but not in multivariate analysis.

The most significant limitations of our study are its retrospective design and relatively low sample size. However, its strengths are that it is a single-centre study, and our follow-up time is relatively long.

In conclusion, surgical margin width and tumor diameter were independently associated with local recurrence. In contrast, patient age, RT boost, hormonotherapy use, and poor histological features were not significantly associated with local recurrence.

Conflict of interests

The authors declare no conflict of interests.

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